Is DNA immunization the following generation of hepatitis B vaccine?

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Sir - Immunization with naked DNA expressing infectious agents antigens is a novel and promising direction in vaccinology. However, every new developing vaccine against certain infection presents some specificity that have to be considered. Is DNA based vaccine an actual candidate to replace existing hepatitis B vaccines?

Plasma-derived and recombinant variants of Hepatitis B vaccines have shown high rate of safety and efficacy. Nevertheless, the innocuousness of nucleic acid immunization is still controversial. Besides the main problem concerning the safety of DNA vaccines discussed in literature1, other aspects might be concern to the safety, efficacy and cost of Hepatitis B vaccines.

The presence of oncogenic virus promoters like CMV or SV40 is potentially dangerous and the 3′-nontranslated region of HBV genome used as signal for transcription termination and polyadenilation2 contains sequences recognized as enhancers and initiators of recombination. The role of preS epitopes to raise the potency of HBV particles-based vaccines is well known. Notwithstanding, preS2-S nucleotide sequence can be modified during integration and become transactivator of cellular genes3.

Integration of HBV DNA is considered to be a step of the mechanism for induction to chronic disease and carcinogenesis. As Hepatitis B vaccine has to be administered to babies who are several times more susceptible to develop a chronic disease than adults, clinical trials in children at early age can be a risk, considering the potentiality of HBV-DNA integration of transactivation. It is considered that DNA integration should be a rare event in DNA immunization since episomal DNA is transfected to nondenying nucleic cells. However, there is an actual chance of injected DNA to be spread and taken up by tissues where cells are dividing, giving an opportunity to HBV DNA to be integrated into cellular genome.

Another kind of problem is concerned with permanent synthesis of HBsAg that can
be over-sufficient to elicit antibodies and lead to an uncontrolled and irreversible chronic-like status (antigenemia).

Intramuscular injections as a method of administration of DNA-based vaccines has to be improved. In our experiments 180 mice injected with different plasmids (which expressed HBsAg in mammalian cultures) in varied concentrations, by single and multi-injection schedules, elicited weak immune answers, measured by seroconversion and anti-HBs GMT, in comparison to 1 g of yeast-derived vaccines (Engerix B and BUTANG 1). Similar results were obtained in rabbits as reported by Dr. J. R. Pinho in the Virology Congress - Ribeirão Preto - SP, Brazil, (26-29 November, 1995). Probably muscle tissue regeneration is of crucial importance for HBV DNA immunization as shown before. However, regeneration induced by toxin treatment can not be used for human applications.

Surely for the development of new biological products for massive use, not only the efficiency but the cost of them have to be carefully analyzed and not simply announced in a published phrase: "Instead of putting your DNA into yeast cells and going through the laborious process of production and purification, you put the DNA right into [the subjects to be vaccinate], avoiding the intervening steps". Considering the amount of FNA to be effectively injected into human muscle, not less than 500 g (which was published as rabbit's dose), how to produce millions of doses of this vaccine without utilizing large-scale production? How to keep away from fermentation processes, purification methods that has to result in no more than 100 pg of E.coli residual DNA per nucleic acid vaccine dose (WHO requirements) and other "intervening steps"? Analysis based on working pilot plant figures shows no significant economical advantage of E.coli-derived DNA-based vaccine in doses higher than 100 g in comparison to yeast-derived HBsAg-based vaccine in doses of 10-20 g.

Thus, nucleic acid immunization might be a new approach of great value to overcome the inaccessibility or low immunogenicity of some antigens other than recombinant HBsAg which has been used as a stable, effective and safe vaccine.

REFERENCES


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